REMARKS

Claims 1, 117-166 and 170-174 were pending in the present application. With this Amendment, claims 127-128, 130-132, 137, 139, 142-146, 149 and 164-166 have been cancelled without prejudice. With this Amendment, new claims 175-178 have been added and claims 1, 121, 138, 159 and 174 have been amended. Upon entry of the present amendments, claims 1, 117-126, 133-136, 138, 140-141, 147-148, 150-163 and 170-178 will be pending.

Support for substantive claims amendments is set forth in the following table:

Claim Number	Support for Amendments in WO 2005/013090 A2
1. (Currently amended) A method for constructing a variant set for modifying a biopolymer of interest, the method comprising: a) identifying a plurality of positions in said biopolymer of interest and, for each respective position in said plurality of positions, one or more substitutions for the respective position, wherein the plurality of positions and the one or more substitutions for each respective position in the plurality of positions collectively define a biopolymer sequence space; b) selecting a first plurality of variants of the biopolymer of interest thereby forming a variant set, wherein said variant set comprises a subset of said biopolymer sequence space, c) measuring a property of all or a portion of the variants in the variant set; and d) modeling a sequence-activity relationship between (i) one or more substitutions at one or more positions of the biopolymer of interest represented by the variant set and (ii) the property measured for all or the portion of the variants in the variant set, wherein the sequence-activity relationship <u>has the form</u> $$\underline{Y = f(w_1x_1, w_2x_2, \ldots w_ix_i)}$$ <u>wherein,</u> <u>Y is a quantitative measure of the property;</u> <u>x_i is a descriptor of a substitution, a combination of substitutions, or a principal component of one or more substitutions, at one or more positions in the plurality of positions;</u> <u>w_i is a weight applied to the descriptor x_i; and</u> <u>f( ) is a mathematical function,</u>	Page 12, lines 21-29; claim 52 as originally filed

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Claim Number	Support for Amendments in WO 2005/013090 A2
~~comprises a plurality of weight functions~~ and wherein the modeling comprises: i) ~~modeling~~ optimizing [[a]] the sequence-activity relationship ~~between (i) one or more substitutions at one or more positions of the biopolymer of interest represented by the variant set and (ii) the property measured for the variants in the variant set, wherein either (1) individual variants and the property measured for the individual variants is left out of the modeling i) on a randomly selected basis or (2) individual positions of the biopolymer of interest are left out of the modeling i) on a randomly selected basis~~ by adjusting individual weights w_i for each said descriptor x_i using a refinement algorithm that minimizes the difference between the predicted values and the real values of Y from partial data,	Page 70, lines 6-31, where the term "property" (Y) is further defined in Section 5.9 beginning on page 104, line 10
wherein the partial data is the first plurality of variants with either (i) individual sequences left out on a random basis or (ii) individual substitutions at positions in the plurality of positions left out on a random basis,	Page 72, lines 15-18 ("Either individual sequences and their associated activities or individual substitution positions can be left out. A sequence-activity relationship can then be constructed from this partial data."); page 72, lines 18-19 ("each time the data to leave out is selected randomly")
ii) repeating the optimizing ~~modeling~~ i) a plurality of times thereby obtaining, for each respective substitution or combination of substitutions x_i, (a) an average value for the weight w_i describing a relative or absolute	Page 72, lines 17-19 ("A sequence-activity relationship can then be constructed from

Claim Number	Support for Amendments in WO 2005/013090 A2
contribution of the respective substitution or combination of substitutions x_i to Y, and (b) a standard deviation, variance or other measure of confidence in the weight w_i describing the relative or absolute contribution of the respective substitution or combination of substitutions x_i to Y; a plurality of values for each weight function in the plurality of weight functions, and iii) using the plurality of values for each weight function in the plurality of weight functions to calculate an average and range of values for each weight function in the plurality of weight functions.	this partial data. This process can be repeated many times, each time the data to leave out is selected randomly."); page 74, line 27, through page 75, line 2, ("In some embodiments, average values (or some other mathematical function of two or more values derived by two or more sequence-activity models) can be calculated for the regression coefficient, weight or other value describing the relative or absolute contribution of each substitution or combination of substitutions to one or more activity of the biopolymer" "In some embodiments, the standard deviation, variance or other measure of confidence with which the value describing the contribution of the substitution or combination of substitutions to one or more activity of the biopolymer can be assigned)

Claim Number	Support for Amendments in WO 2005/013090 A2

138. (Previously presented) The method of claim <u>1</u> ~~17~~, wherein the modeling comprises <u>least square regression, linear regression, non-linear regression, logistic regressing, or partial least squares projection to latent variables</u> ~~regressing:~~
 	
~~V~~_{~~measured~~} ~~= W₁₁P₁S₁ + W₁₂P₁S₂ + … + W₁ₙP₁Sₙ + …+ W_M₁P_MS₁ + W_M₂P_MS₂ + … + W_MNP_MSₙ~~
 	
~~wherein,~~
    ~~V_measured represents the property measured in variants in the variant set;~~
    ~~W_MN = is a value in the plurality of values;~~
    ~~P_M = is a descriptor of a position in the biopolymer of interest in the plurality of positions in the biopolymer of interest; and~~
    ~~Sₙ = is a descriptor of a substitution in the one or more positions for a position in the plurality of positions in the biopolymer of interest.~~
	Page 70, lines 8-11; page 13, lines 1-2

175. (New) The method of claim 1 wherein the function f is a linear combination of the x_i and the sequence-activity relationship has the form: $$Y = w_1x_1 + w_2x_2, + \dots w_ix_i.$$	Page 63, lines 28-32
176. (New) The method of claim 117 wherein a respective x_i in the sequence-activity relationship is a descriptor of a substitution or a combination of substitutions and wherein the substitution or combination of substitutions is selected for the new variant set for the biopolymer of interest when the weight w_i corresponding to the respective x_i is positive.	Page 77, lines 9-22
177. (New) The method of claim 176 wherein the weight w_i corresponding to the respective x_i is at least one standard deviation above neutrality.	Page 77, lines 19-26
178. (New) The method of claim 176 wherein the substitution or combination of substitutions has been tested at least three	Page 77, lines 23-27

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times.	

Accordingly, no new matter has been introduced by way of claim amendment.

Restriction Requirement

In the Office Action mailed January 4, 2010, the Examiner imposed a Restriction Requirement requiring election of one of the following two groups of claims:

I: Claims 1, 117-166 and 170-174 drawn to a method of constructing a variant set for modifying a biopolymer of interest and a computer program product for performing the method; and

II: Claims 167-169, drawn to a nucleic acid sequence or a cell comprising the same.

The Examiner contends that the above groups are distinct, each from the other. In response, Applicants hereby elect Group I, claims 1, 117-126, 133-136, 138, 140-141, 147-148, 150-163 and 170-174. Applicants respectfully submit that new claims 175-178 fall within elected Group I.

SPECIES ELECTION

In view of the claim amendments presented in this Amendment, Applicants have reviewed the Election Requirements set forth in the Office Action mailed July 27, 2009 to identify which claims remain generic to, and which claims read on, the species elections that were required in the July 27, 2009 Office Action. As set forth below, Applicants note that in view of the claim amendments made in this Amendment, the Third Species Election Requirement should be withdrawn.

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First Species Election Requirement

In the Office Action mailed July 27, 2009, the Examiner imposed the following species election requirement:

Species 1A   The modeling comprises computation of a neural network, a Bayesian model, a generalized additive model, a support vector machine, machine learning or classification using a regression tree, as in claim 140; or

Species 1B   The modeling comprises boosting or adaptive boosting, as in claim 141.

In Applicants' October 19, 2009 response to the July 27, 2009 Office Action, Applicants provisionally elected, with traverse, Species 1A.

With this Amendment, claims 1, 117-126, 129, 133-136, 138, 140, 147-148, 150-163 and 170-178 are believed to be readable upon elected species 1A. Claims 1, 117-126, 129, 133-136, 138, 147-148, 150-163 and 170-178 are believed to be generic to elected species 1A.

Second Species Election Requirement

In the Office Action mailed July 27, 2009, the Examiner imposed the following additional species election requirement:

Species 2A   The biopolymer is one of those listed in claim 151; or

Species 2B   The biopolymer is one of those listed in claim 152.

In Applicants' October 19, 2009 response to the July 27, 2009 Office Action, Applicants provisionally elected, with traverse, Species 2B.

With this Amendment, claims 1, 117-126, 133-136, 138, 140-141, 147-148, 150, 152-163 and 170-178 are believed to be readable upon elected species 2B. Claims 1, 117-126, 133-136, 138, 140-141, 147-148, 150, 153-163 and 170-178 are believed to be generic to elected species 2B.

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Third Species Election Requirement

In the Office Action mailed July 27, 2009, the Examiner imposed the following additional species election requirement:

Species 3A   The modeling comprises regressing using the equation as stated in claim 138; or

Species 3B   The modeling comprises regressing using the equation as stated in claim 165.

In Applicants' October 19, 2009 response to the July 27, 2009 Office Action, Applicants provisionally elected, with traverse, Species 3B. Applicants respectfully submit that the pending claims no longer recite the regression equation of claims 138 or 165. In fact, claim 165 has been cancelled. Thus, Applicants respectfully submit that the third species election in the July 27, 2009 Office Action should be withdrawn in light of Applicants' claim amendments.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks into the file of the above-identified application. If any fees are due in connection with this submission, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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